CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 040189

Trade Name : METHYLPREDNISOLONE TABLETS USP

Generic Name: Methylprednisolone Tablets USP 4mg and 8mg

Sponsor : Trigen Laboratories ,Inc.

Approval Date: October 31, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 040189

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
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Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
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Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 040189

APPROVAL LETTER

ANDA 40-189

OCT 31 1997

Trigen Laboratories, Inc.
Attention: Rajan Embran
207 Kiley Drive
Salisbury, MD 21801

Dear Sir:

This is in reference to your abbreviated new drug application dated May 24, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Methylprednisolone Tablets USP, 4 mg and 8 mg.

Reference is also made to your amendments dated June 27, August 7 and 20, and October 21, and 31, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Methylprednisolone Tablets USP, 4 mg and 8 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Medrol® Tablets, 4 mg and 8 mg, respectively, of The Pharmacia and Upjohn Company). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

10/31/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040189

FINAL PRINTED LABELING

NDC 59746-001-06

METHYLPREDNISOLONE TABLETS USP

4 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

Trigen Laboratories, Inc.
Salisbury, MD 21801

See package insert for complete product information.
Dispense in tight, light resistant container.
Keep patient under close observation of a physician.
Store at controlled room temperature 15°-30° C (59°-86° F).

N 3 59746-001-06 3

REV. 6/97

LOT:
EXP: Sample

NDC 59746-001-09

METHYLPREDNISOLONE TABLETS USP

4 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 Tablets

Trigen Laboratories, Inc.
Salisbury, MD 21801

See package insert for complete product information.
Dispense in tight, light resistant container.
Keep patient under close observation of a physician.
Store at controlled room temperature 15°-30° C (59°-86° F).

N 3 59746-001-09 4

REV. 6/97

LOT:
EXP: Sample

NDC 59746-002-04

METHYLPREDNISOLONE TABLETS USP

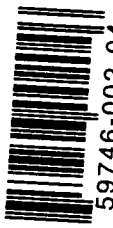
8 mg

CAUTION: Federal law prohibits dispensing without prescription.

25 Tablets

Trigen Laboratories, Inc.
Salisbury, MD 21801

See package insert for complete product information.
Dispense in tight, light resistant container.
Keep patient under close observation of a physician.
Store at controlled room temperature 15°-30° C (59°-86° F).



REV. 6/97

LOT:
EXP:

Sample

NDC 59746-002-06

METHYLPREDNISOLONE TABLETS USP

8 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

Trigen Laboratories, Inc.
Salisbury, MD 21801

See package insert for complete product information.
Dispense in tight, light resistant container.
Keep patient under close observation of a physician.
Store at controlled room temperature 15°-30° C (59°-86° F).

REV. 6/97

LOT:
EXP:

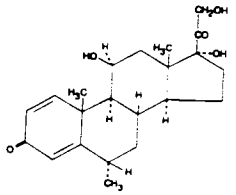
Sample

METHYLPREDNISOLONE TABLETS, USP

DESCRIPTION

Methylprednisolone Tablets contain methylprednisolone which is a glucocorticoid. Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastrointestinal tract. Methylprednisolone occurs as a white to practically white, odorless, crystalline powder. It is sparingly soluble in alcohol, in dioxane, and in methanol, slightly soluble in acetone, and in chloroform, and very slightly soluble in ether. It is practically insoluble in water.

The chemical name for methylprednisolone is pregna-1,4-diene-3,20-dione, 11, 17, 21-trihydroxy-6-methyl-, (6α,11β)- and the molecular weight is 374.48. The structural formula is represented below:



$C_{22}H_{30}O_5$

Methylprednisolone Tablets, for oral administration, are available as scored tablets in the following strengths: 4 mg and 8 mg. In addition each tablet contains the following inactive ingredients: lactose anhydrous, sodium starch glycolate, microcrystalline cellulose, sodium lauryl sulfate, colloidal silicon dioxide, pregelatinized starch, and magnesium stearate.

CLINICAL PHARMACOLOGY

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs are primarily used for their potent anti-inflammatory effects in disorders of many organ systems.

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.

INDICATIONS AND USAGE

Methylprednisolone Tablets are indicated in the following conditions:

1. **Endocrine Disorders**
   - Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the first choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy mineralocorticoid supplementation is of particular importance).
   - Congenital adrenal hyperplasia
   - Nonsuppurative thyroiditis
   - Hypercalcemia associated with cancer
2. **Rheumatic Disorders**
   - As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:
   - Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy)
   - Ankylosing spondylitis
   - Acute and subacute bursitis
   - Synovitis of osteoarthritis
   - Acute nonspecific tenosynovitis
   - Post-traumatic osteoarthritis
   - Psoriatic arthritis
   - Epicondylitis
   - Acute gouty arthritis
3. **Collagen Diseases**
   - During an exacerbation or as maintenance therapy in selected cases of:
   - Systemic lupus erythematosus
   - Systemic dermatomyositis (polymyositis)
   - Acute rheumatic carditis
4. **Dermatologic Diseases**
   - Bullous dermatitis herpetiformis
   - Severe erythema multiforme (Stevens-Johnson syndrome)
   - Severe seborrheic dermatitis
   - Exfoliative dermatitis
   - Mycosis fungoides
   - Pemphigus
   - Severe psoriasis
5. **Allergic States**
   - Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment:
   - Seasonal or perennial allergic rhinitis
   - Drug hypersensitivity reactions
   - Serum sickness
   - Contact dermatitis
   - Bronchial asthma
   - Atopic dermatitis
6. **Ophthalmic Diseases**
   - Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as:
   - Allergic corneal marginal ulcers
   - Herpes zoster ophthalmicus
   - Anterior segment inflammation
   - Diffuse posterior uveitis and choroiditis
   - Sympathetic ophthalmia
   - Keratitis
   - Optic neuritis
   - Allergic conjunctivitis
   - Chorioretinitis
   - Iritis and iridocyclitis
7. **Respiratory Diseases**
   - Symptomatic sarcoidosis
   - Berylliosis
   - Loeffler's syndrome not manageable by other means Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy
   - Aspiration pneumonitis
8. **Hematologic Disorders**
   - Idiopathic thrombocytopenic purpura in adults
   - Secondary thrombocytopenia in adults
   - Acquire (autoimmune) hemolytic anemia
   - Erythroblastopenia (RBC anemia)
   - Congenital (erythroid) hypoplastic anemia
9. **Neoplastic Diseases**
   - For palliative management of:
   - Leukemias and lymphomas in adults
   - Acute leukemia of childhood
10. **Edematous States**
    - To induce a diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus.
11. **Gastrointestinal Diseases**
    - To tide the patient over a critical period of the disease in:
    - Ulcerative colitis
    - Regional enteritis
12. **Nervous System**
    - Acute exacerbations of multiple sclerosis
13. **Miscellaneous**
    - Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy.
    - Trichinosis with neurologic or myocardial involvement.

CONTRAINDICATIONS

Systemic fungal infections and known hypersensitivity to components.

WARNINGS

In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Usage in pregnancy: Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy, should be carefully observed for signs of hypoadrenalism.

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

While on corticosteroid therapy patients should not be vaccinated against smallpox. Other immunization procedure should not be undertaken in patients who are on corticosteroids, especially on high dose, because of possible hazards of neurological complications and a lack of antibody response.

The use of Methylprednisolone Tablets in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globuline (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

PRECAUTIONS

General Precautions

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and /or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids on patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection; diverticulitis; fresh intestinal anastomoses; active or latent peptic ulcer; renal insufficiency; hypertension; osteoporosis; and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (see **DOSAGE AND ADMINISTRATION.**)

METHYLPREDNISOLONE TABLETS, USP

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decisions must be made in each individual case as to dose and duration of treatment and as to weather daily or intermittent therapy should be used.

Convulsions have been reported with concurrent use of methylprednisolone and cyclosporine. Since concurrent use of these agents results in a mutual inhibition of metabolism, it is possible that adverse events associated with the individual use of either drug may be more apt to occur.

Information for the Patient

Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles and, if exposed, to obtain medical advice.

ADVERSE REACTIONS

Fluid and Electrolyte Disturbances
Sodium retention
Congestive heart failure in susceptible patients
Hypertension
Fluid retention
Potassium loss
Hypokalemic alkalosis

Musculoskeletal
Muscle weakness
Loss of muscle mass
Steroid myopathy
Osteoporosis
Vertebral compression fractures
Aseptic necrosis of femoral and humeral heads
Pathologic fracture of long bones

Gastrointestinal
Peptic ulcer with possible perforation and hemorrhage
Pancreatitis
Abdominal distention
Ulcerative esophagitis

Dermatologic
Impaired wound healing
Petechiae and ecchymoses
May suppress reactions to skin tests
Thin fragile skin
Facial erythema
Increased sweating

Neurological
Increased intracranial pressure with papilledema
(pseudo-tumor cerebri) usually after treatment
Convulsions
Vertigo
Headache

Endocrine
Development of Cushingoid state
Suppression of growth in children
Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness
Menstrual irregularities
Decreased carbohydrate tolerance
Manifestations of latent diabetes mellitus
Increased requirements for insulin or oral hypoglycemic agents in diabetics

Ophthalmic
Posterior subcapsular cataracts
Increased intraocular pressure
Glaucoma
Exophthalmos

Metabolic
Negative nitrogen balance due to protein catabolism

The following additional reactions have been reported following oral as well as parenteral therapy:
Uticaria and other allergic, anaphylactic or hypersensitivity reactions.

DOSAGE AND ADMINISTRATION

The initial dosage of Methylprednisolone Tablets may vary from 4 mg to 48 mg of methylprednisolone per day depending on the specific disease entity being treated. In situations of less severity lower doses will generally suffice while in selected patients higher initial doses may be required. The initial dosage should be maintained or adjusted until a satisfactory response is noted. If after a reasonable period of time there is a lack of satisfactory clinical response, Methylprednisolone should be discontinued and the patient transferred to other appropriate therapy.

IT SHOULD BE EMPHASIZED THAT DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE UNDER TREATMENT AND THE RESPONSE OF THE PATIENT. After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. It should be kept in mind that constant monitoring is needed in regard to drug dosage. Included in the situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment; in this latter situation it may be necessary to increase the dosage of Methylprednisolone for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

Multiple Sclerosis: In treatment of acute exacerbations of multiple sclerosis daily doses of 200 mg of prednisolone for a week followed by 80 mg every other day for 1 month have been shown to be effective (4 mg of methylprednisolone is equivalent to 5 mg of prednisolone).

ADT (Alternative Day Therapy): Alternative day therapy is a corticosteroid dosing regimen in which twice the usual daily dose of corticoid in administered every other morning. The purpose of this mode of therapy is to provide the patient requiring long-term pharmacologic dose treatment with the beneficial effects of corticoids while minimizing certain undesirable effects, including pituitary-adrenal suppression, the Cushingoid state, Corticoid withdrawal symptoms, and growth suppression in children.

The rationale for this treatment schedule is based on two major premises: (a) the anti-inflammatory or therapeutic effect of corticoids persists longer than their physical presence and metabolic effects and (b) administration of the corticosteroid every other morning allows for reestablishment of more nearly normal hypothalamic-pituitary-adrenal (HPA) activity on the off-steroid day.

A brief review of the HPA physiology may be helpful in understanding this rationale. Acting primarily through the hypothalamus a fall in free cortisol stimulates the pituitary gland to produce increasing amounts of corticotropin (ACTH) while a rise in free cortisol inhibits ACTH secretion. Normally the HPA system is characterized by diurnal (circadian) rhythm. Serum levels of ACTH rise from a low point about 10 pm to a peak level about 6 am. Increasing levels of ACTH stimulate adrenal cortical activity resulting in a rise in plasma cortisol with maximal levels occurring between 2 am and 8 am. This rise in cortisol dampens ACTH production and in turn adrenal cortical activity. There is a gradual fall in plasma corticoids during the day with lowest levels occurring about midnight.

The diurnal rhythm of the HPA axis is lost in Cushing's disease, a syndrome of adrenal cortical hyperfunction characterized by obesity with centripetal fat distribution, thinning of the skin with easy bruisability, muscle wasting with weakness, hypertension, latent diabetes, osteoporosis, electrolyte imbalance, etc. The same clinical findings of hyperadrenocorticism may be noted during long-term pharmacologic dose corticoid therapy administered in conventional daily divided doses. It would appear, then, that a disturbance in the diurnal cycle with maintenance of elevated corticoid values during the night may play a significant role in the development of undesirable corticoid effects. Escape from these constantly elevated plasma levels for even short periods of time may be instrumental in protecting against undesirable pharmacologic effects.

During conventional pharmacologic dose corticosteroid therapy, ACTH production is inhibited with subsequent suppression of cortisol production by the adrenal cortex. Recovery time for normal HPA activity is variable depending upon the dose and duration of treatment. During this time the patient is vulnerable to any stressful situation. Although it has been shown that there is considerably less adrenal suppression following a single morning dose of prednisolone (10 mg) as opposed to a quarter of that dose administered every six hours, there is evidence that some suppressive effect on adrenal activity may be carried over into the following day when pharmacologic doses are used. Further, it has been shown that a single dose of certain corticosteroids will produce adrenal cortical suppression for two or more days. Other corticoids, including methylprednisolone, hydrocortisone, prednisone, and prednisolone, are considered to be short acting (producing adrenal cortical suppression for $1\frac{1}{4}$ to $1\frac{1}{2}$ days following a single dose) and thus are recommended for alternate day therapy.

The following should be kept in mind when considering alternate day therapy:

1) Basic principles and indications for corticosteroid therapy should apply. The benefits of ADT should not encourage the indiscriminate use of steroids.

2) ADT is a therapeutic technique primarily designed for patients in whom long-term pharmacologic corticoid therapy is anticipated.

3) In less severe disease processes in which corticoid therapy is indicated, it may be possible to initiate treatment with ADT. More severe disease states usually will require daily divided high dose therapy for initial control of the disease process. The initial suppressive dose level should be continued until satisfactory clinical response is obtained, usually four to ten days in the case of many allergic and collagen diseases. It is important to keep the period of initial suppressive dose as brief as possible particularly when subsequent use of alternate day therapy is intended.

   Once control has been established, two courses are available: (a) change a ADT and then gradually reduce the amount of corticoid given every other day or (b) following control of the disease process reduce the daily dose of corticoid to the lowest effective level as rapidly as possible and then change over to an alternate day schedule. Theoretically, course (a) may be preferable.

4) Because of the advantages of ADT, it may be desirable to try patients on this form of therapy who have been on daily corticoids for long periods of time (eg, patients with rheumatoid arthritis). Since these patients may already have a suppressed HPA axis, established them on ADT may be difficult and not always successful. However, it is recommended that regular attempts be made to change them over. It may be helpful to triple or even quadruple the daily maintenance dose and administer this every other day rather than just doubling the daily dose if difficulty is encountered. Once the patient is again controlled, an attempt should be made to reduce this dose to a minimum.

5) As indicated above, certain corticosteroids, because of their prolonged suppressive effect on adrenal activity, are not recommended for alternate day therapy (eg, dexamethasone and betamethasone).

6) The maximal activity of the adrenal cortex is between 2 am and 8 am, and it is minimal between 4 pm and midnight. Exogenous corticosteroids suppress adrenocortical activity the least, when given at the time of maximal activity (am).

7) In using ADT it is important, as in all therapeutic situations to individualize and tailor the therapy to each patient. Complete control of symptoms will not be possible in all patients. An explanation of the benefits of ADT will help the patient to understand and tolerate the possible flare-up in symptoms which may occur in the latter part of the off-steroid day. Other symptomatic therapy may be added or increased at this time if needed.

8) In the event of an acute flare-up of the disease process, it may be necessary to return to a full suppressive daily divided corticoid dose for control. Once control is again established alternate day therapy may be reinstituted.

9) Although many of the undesirable features of corticosteroid therapy can be minimized by ADT, as in any therapeutic situation, the physician must carefully weigh the benefit-risk ratio for each patient in whom corticoid therapy is being considered.

HOW SUPPLIED

Methylprednisolone Tablets are available in the following strengths and package sizes:

4 mg (white, oval, scored, imprinted TL 001)

Bottles of 100	NDC 59746-001-06
Bottles of 500	NDC 59746-001-09
Unit of use pack (21 tablets)	NDC 59746-001-03

8 mg (white, oval, scored, imprinted TL 002)

Bottles of 25	NDC 59746-002-04
Bottles of 100	NDC 59746-002-06

Store at controlled room temperature 15° to 30° C (59° to 86° F)

CAUTION: Federal Law prohibits dispensing without prescription.

Trigen Laboratories, Inc.
Salisbury, MD 21801, USA
Revised June 1997

[redacted] Trigen

001

NDC 59746-001-03

21 Tablets Unit of Use

Methylprednisolone Tablets, USP

4 mg

Keep patient under close observation of a physician.

See package insert for complete product information.

Store at controlled room temperature
15° to 30°C (59° to 86°F).

Caution: Federal law prohibits dispensing without prescription.

Rev. 6/97

LOT:

EXP:

Trigen Laboratories, Inc.
Salisbury, MD 21801, USA

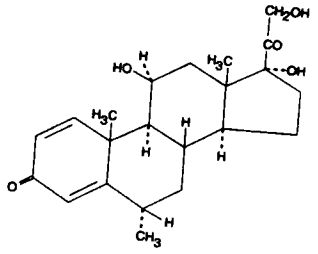
59746-001-03 2

METHYLPREDNISOLONE TABLETS, USP

DESCRIPTION

Methylprednisolone Tablets contain methylprednisolone which is a glucocorticoid. Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastrointestinal tract. Methylprednisolone occurs as a white to practically white, odorless, crystalline powder. It is sparingly soluble in alcohol, in dioxane, and in methanol, slightly soluble in acetone, and in chloroform, and very slightly soluble in ether. It is practically insoluble in water.

The chemical name for methylprednisolone is pregna-1,4-diene-3,20-dione, 11, 17, 21-trihydroxy-6-methyl-,(6α,11β)- and the molecular weight is 374.48. The structural formula is represented below:



$C_{22}H_{30}O_5$

Methylprednisolone Tablets, for oral administration, are available as scored tablets in the following strengths: 4 mg and 8 mg. In addition each tablet contains the following inactive ingredients: lactose anhydrous, sodium starch glycolate, microcrystalline cellulose, sodium lauryl sulfate, colloidal silicon dioxide, pregelatinized starch, and magnesium stearate.

CLINICAL PHARMACOLOGY

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs are primarily used for their potent anti-inflammatory effects in disorders of many organ systems.

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.

INDICATIONS AND USAGE

Methylprednisolone Tablets are indicated in the following conditions:

1. Endocrine

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune response to diverse stimuli.

INDICATIONS AND USAGE

Methylprednisolone Tablets are indicated in the following conditions:

1. **Endocrine Disorders**
   Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the first choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy mineralocorticoid supplementation is of particular importance).
   Congenital adrenal hyperplasia
   Nonsuppurative thyroiditis
   Hypercalcemia associated with cancer

2. **Rheumatic Disorders**
   As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:
   Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy)
   Ankylosing spondylitis
   Acute and subacute bursitis
   Synovitis of osteoarthritis
   Acute nonspecific tenosynovitis
   Post-traumatic osteoarthritis
   Psoriatic arthritis
   Epicondylitis
   Acute gouty arthritis

3. **Collagen Diseases**
   During an exacerbation or as maintenance therapy in selected cases of:
   Systemic lupus erythematosus
   Systemic dermatomyositis (polymyositis)
   Acute rheumatic carditis

4. **Dermatologic Diseases**
   Bullous dermatitis herpetiformis
   Severe erythema multiforme (Stevens-Johnson syndrome)
   Severe seborrheic dermatitis
   Exfoliative dermatitis
   Mycosis fungoides
   Pemphigus
   Severe psoriasis

5. **Allergic States**
   Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment:
   Seasonal or perennial allergic rhinitis
   Drug hypersensitivity reactions
   Serum sickness
   Contact dermatitis
   Bronchial asthma
   Atopic dermatitis

6. **Ophthalmic Diseases**
   Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as:
   Allergic corneal marginal ulcers
   Herpes zoster ophthalmicus
   Anterior segment inflammation
   Diffuse posterior uveitis and choroiditis
   Sympathetic ophthalmia
   Keratitis
   Optic neuritis
   Allergic conjunctivitis
   Chorioretinitis
   Iritis and iridocyclitis

7. **Respiratory Diseases**
   Symptomatic sarcoidosis
   Berylliosis
   Loeffler's syndrome not manageable by other means Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy
   Aspiration pneumonitis

8. **Hematologic Disorders**
   Idiopathic thrombocytopenic purpura in adults
   Secondary thrombocytopenia in adults
   Acquire (autoimmune) hemolytic anemia
   Erythroblastopenia (RBC anemia)
   Congenital (erythroid) hypoplastic anemia

9. **Neoplastic Diseases**
   For palliative management of:
   Leukemias and lymphomas in adults
   Acute leukemia of childhood

10. **Edematous States**
    To induce a diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus.

11. **Gastrointestinal Diseases**
    To tide the patient over a critical period of the disease in:
    Ulcerative colitis
    Regional enteritis

12. **Nervous System**
    Acute exacerbations of multiple sclerosis

13. **Miscellaneous**
    Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy.
    Trichinosis with neurologic or myocardial involvement.

CONTRAINDICATIONS

Systemic fungal infections and known hypersensitivity to components.

WARNINGS

In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

... of infection, and new infections may appear during their use. The ...

concurrently with appropriate antituberculous chemotherapy
Aspiration pneumonitis

8. Hematologic Disorders
Idiopathic thrombocytopenic purpura in adults
Secondary thrombocytopenia in adults
Acquire (autoimmune) hemolytic anemia
Erythroblastopenia (RBC anemia)
Congenital (erythroid) hypoplastic anemia

9. Neoplastic Diseases
For palliative management of:
Leukemias and lymphomas in adults
Acute leukemia of childhood

10. Edematous States
To induce a diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus.

11. Gastrointestinal Diseases
To tide the patient over a critical period of the disease in:
Ulcerative colitis
Regional enteritis

12. Nervous System
Acute exacerbations of multiple sclerosis

13. Miscellaneous
Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy.
Trichinosis with neurologic or myocardial involvement.

CONTRAINDICATIONS

Systemic fungal infections and known hypersensitivity to components.

WARNINGS

In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Usage in pregnancy: Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy, should be carefully observed for signs of hypoadrenalism.

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

While on corticosteroid therapy patients should not be vaccinated against smallpox. Other immunization procedure should not be undertaken in patients who are on corticosteroids, especially on high dose, because of possible hazards of neurological complications and a lack of antibody response.

The use of Methylprednisolone Tablets in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globuline (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

PRECAUTIONS

General Precautions

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and /or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids on patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection; diverticulitis; fresh intestinal anastomoses; active or latent peptic ulcer; renal insufficiency; hypertension; osteoporosis; and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (see **DOSAGE AND ADMINISTRATION.**)

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decisions must be made in each individual case as to dose and duration of treatment and as to weather daily or intermittent therapy should be used.

Convulsions have been reported with concurrent use of methylprednisolone and cyclosporine. Since concurrent use of these agents results in a mutual inhibition of metabolism, it is possible that adverse events associated with the individual use of either drug may be more apt to occur.

Information for the Patient

Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles and, if exposed, to obtain medical advice.

ADVERSE REACTIONS

Fluid and Electrolyte Disturbances
Sodium retention
Congestive heart failure in susceptible patients
Hypertension
Fluid retention
Potassium loss
Hypokalemic alkalosis

Musculoskeletal
Muscle weakness
Loss of muscle mass
Steroid myopathy
Osteoporosis
Vertebral compression fractures
Aseptic necrosis of femoral and humeral heads
Pathologic fracture of long bones

Gastrointestinal
Peptic ulcer with possible perforation and hemorrhage
Pancreatitis
Abdominal distention
Ulcerative esophagitis

Dermatologic
Impaired wound healing
Petechiae and ecchymoses
May suppress reactions to skin tests
Thin fragile skin
Facial erythema
Increased sweating

Neurological
Increased intracranial pressure with papilledema
(pseudo-tumor cerebri) usually after treatment
Convulsions
Vertigo
Headache

Endocrine
Development of Cushingoid state
Suppression of growth in children
Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness
Menstrual irregularities
Decreased carbohydrate tolerance
Manifestations of latent diabetes mellitus
Increased requirements for insulin or oral hypoglycemic agents in diabetics

Ophthalmic
Posterior subcapsular cataracts
Increased intraocular pressure
Glaucoma
Exophthalmos

Metabolic
Negative nitrogen balance due to protein catabolism

The following additional reactions have been reported following oral as well as parenteral therapy:
Uticaria and other allergic, anaphylactic or hypersensitivity reactions.

DOSAGE AND ADMINISTRATION

The initial dosage of Methylprednisolone Tablets may vary from 4 mg to 48 mg of methylprednisolone per day depending on the specific disease entity being treated. In situations of less severity lower doses will generally suffice while in selected patients higher initial doses may be required. The initial dosage should be maintained or adjusted until a satisfactory response is noted. If after a reasonable period of time there is a lack of satisfactory clinical response, Methylprednisolone should be discontinued and the patient transferred to other appropriate therapy.

IT SHOULD BE EMPHASIZED THAT DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE UNDER TREATMENT AND THE RESPONSE OF THE PATIENT. After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. It should be kept in mind that constant monitoring is needed in regard to drug dosage. Included in the situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment; in this latter situation it may be necessary to increase the dosage of Methylprednisolone for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

Multiple Sclerosis: In treatment of acute exacerbations of [illegible]

Vertigo
Headache

Endocrine
Development of Cushingoid state
Suppression of growth in children
Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness
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Multiple Sclerosis: In treatment of acute exacerbations of multiple sclerosis daily doses of 200 mg of prednisolone for a week followed by 80 mg every other day for 1 month have been shown to be effective (4 mg of methylprednisolone is equivalent to 5 mg of prednisolone).

ADT (Alternative Day Therapy): Alternative day therapy is a corticosteroid dosing regimen in which twice the usual daily dose of corticoid in administered every other morning. The purpose of this mode of therapy is to provide the patient requiring long-term pharmacologic dose treatment with the beneficial effects of corticoids while minimizing certain undesirable effects, including pituitary-adrenal suppression, the Cushingoid state, Corticoid withdrawal symptoms, and growth suppression in children.

The rationale for this treatment schedule is based on two major premises: (a) the anti-inflammatory or therapeutic effect of corticoids persists longer than their physical presence and metabolic effects and (b) administration of the corticosteroid every other morning allows for reestablishment of more nearly normal hypothalamic-pituitary-adrenal (HPA) activity on the off-steroid day.

A brief review of the HPA physiology may be helpful in understanding this rationale. Acting primarily through the hypothalamus a fall in free cortisol stimulates the pituitary gland to produce increasing amounts of corticotropin (ACTH) while a rise in free cortisol inhibits ACTH secretion. Normally the HPA system is characterized by diurnal (circadian) rhythm. Serum levels of ACTH rise from a low point about 10 pm to a peak level about 6 am. Increasing levels of ACTH stimulate adrenal cortical activity resulting in a rise in plasma cortisol with maximal levels occurring between 2 am and 8 am. This rise in cortisol dampens ACTH production and in turn adrenal cortical activity. There is a gradual fall in plasma corticoids during the day with lowest levels occurring about midnight.

The diurnal rhythm of the HPA axis is lost in Cushing's disease, a syndrome of adrenal cortical hyperfunction characterized by obesity with centripetal fat distribution, thinning of the skin with easy bruisability, muscle wasting with weakness, hypertension, latent diabetes, osteoporosis, electrolyte imbalance, etc. The same clinical findings of hyperadrenocorticism may be noted during long-term pharmacologic dose corticoid therapy administered in conventional daily divided doses. It would appear, then, that a disturbance in the diurnal cycle with maintenance of elevated corticoid values during the night may play a significant role in the development of undesirable corticoid effects. Escape from these constantly elevated plasma levels for even short periods of time may be instrumental in protecting against undesirable pharmacologic effects.

During conventional pharmacologic dose corticosteroid therapy, ACTH production is inhibited with subsequent suppression of cortisol production by the adrenal cortex. Recovery time for normal HPA activity is variable depending upon the dose and duration of treatment. During this time the patient is vulnerable to any stressful situation. Although it has been shown that there is considerably less adrenal suppression following a single morning dose of prednisolone (10 mg) as opposed to a quarter of that dose administered every six hours, there is evidence that some suppressive effect on adrenal activity may be carried over into the following day when pharmacologic doses are used. Further, it has been shown that a single dose of certain corticosteroids will produce adrenal cortical suppression for two or more days. Other corticoids, including methylprednisolone, hydrocortisone, prednisone, and prednisolone, are considered to be short acting (producing adrenal cortical suppression for $1\frac{1}{4}$ to $1\frac{1}{2}$ days following a single dose) and thus are recommended for alternate day therapy.

The following should be kept in mind when considering alternate day therapy:

1) Basic principles and indications for corticosteroid therapy should apply. The benefits of ADT should not encourage the indiscriminate use of steroids.

2) ADT is a therapeutic technique primarily designed for patients in whom long-term pharmacologic corticoid therapy is anticipated.

3) In less severe disease processes in which corticoid therapy is indicated, it may be possible to initiate treatment with ADT. More severe disease states usually will require daily divided high dose therapy for initial control of the disease process. The initial suppressive dose level should be continued until satisfactory clinical response is obtained, usually four to ten days in the case of many allergic and collagen diseases. It is important to keep the period of initial suppressive dose as brief as possible particularly when subsequent use of alternate day therapy is intended.

   Once control has been established, two courses are available: (a) change a ADT and then gradually reduce the amount of corticoid given every other day or (b) following control of the disease process reduce the daily dose of corticoid to the lowest effective level as rapidly as possible and then change over to an alternate day schedule. Theoretically, course (a) may be preferable.

4) Because of the advantages of ADT, it may be desirable to try patients on this form of therapy who have been on daily corticoids for long periods of time (eg, patients with rheumatoid arthritis). Since these patients may already have a suppressed HPA axis, established them on ADT may be difficult and not always successful. However, it is recommended that regular attempts be made to change them over. It may be helpful to triple or even quadruple the daily maintenance dose and administer this every other day rather than just doubling the daily dose if difficulty is encountered. Once the patient is again controlled, an attempt should be made to reduce this dose to a minimum.

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5) As indicated above, certain corticosteroids, because of their prolonged suppressive effect on adrenal activity, are not recommended for alternate day therapy (eg, dexamethasone and betamethasone).

6) The maximal activity of the adrenal cortex is between 2 am and 8 am, and it is minimal between 4 pm and midnight. Exogenous corticosteroids suppress adrenocortical activity the least, when given at the time of maximal activity (am).

7) In using ADT it is important, as in all therapeutic situations to individualize and tailor the therapy to each patient. Complete control of symptoms will not be possible in all patients. An explanation of the benefits of ADT will help the patient to understand and tolerate the possible flare-up in symptoms which may occur in the latter part of the off-steroid day. Other symptomatic therapy may be added or increased at this time if needed.

8) In the event of an acute flare-up of the disease process, it may be necessary to return to a full suppressive daily divided corticoid dose for control. Once control is again established alternate day therapy may be reinstituted.

9) Although many of the undesirable features of corticosteroid therapy can be minimized by ADT, as in any therapeutic situation, the physician must carefully weigh the benefit-risk ratio for each patient in whom corticoid therapy is being considered.

HOW SUPPLIED

Methylprednisolone Tablets are available in the following strengths and package sizes:

4 mg (white, oval, scored, imprinted TL 001)

Bottles of 100	NDC 59746-001-06
Bottles of 500	NDC 59746-001-09
Unit of use pack (21 tablets)	NDC 59746-001-03

8 mg (white, oval, scored, imprinted TL 002)

Bottles of 25	NDC 59746-002-04
Bottles of 100	NDC 59746-002-06

Store at controlled room temperature 15° to 30° C (59° to 86° F)

CAUTION: Federal Law prohibits dispensing without prescription.

Trigen Laboratories, Inc.
Salisbury, MD 21801, USA
Revised June 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040189

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 40-189

3. NAME AND ADDRESS OF APPLICANT
Trigen Laboratories, Inc.
Attention: Rajan Embran
207 Kiley Drive
Salisbury, MD 21801

4. LEGAL BASIS FOR SUBMISSION
Approved Drug Product, Medrol® Tablets USP 4 mg & 8 mg.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Methylprednisolone Tablets, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Application Submission Date May 24, 1996
Refuse To File Letter Issue Date June 13, 1996
Amendment Date August 6, 1996
Acceptable for Filing Letter Issue Date August 7, 1996
Minor Amendment Date March 14, 1997.
Minor Amendment Date June 27, 1997 (This Review).

10. PHARMACOLOGICAL CATEGORY
Synthetic Glucocorticoid, Primary
Use as an Antiinflammatory Agent in
Disorders of Many Organ Systems.

11. Rx or OTC
Rx

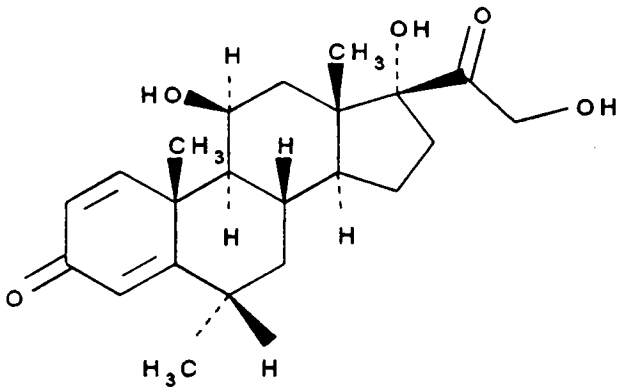
12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Tablets, Oral

14. POTENCY
4 mg & 8 mg

15. CHEMICAL NAME AND STRUCTURE

Methylprednisolone USP
$C_{22}H_{30}O_5$; M.W. = 374.48



11β,17,21-Trihydroxy-6α-methylpregna-1,4-diene-3,20-dione.
CAS [83-43-2]

16. RECORDS AND REPORTS
N/A

17. COMMENTS
See individual review sections; comments from the deficiency letter are followed by firm's response.

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable

REVIEWER:
U. S. Atwal

DATE COMPLETED:
July 31, 1997

cc: ANDA 40-189
DUP Jacket
Division File
Field Copy

Endorsements:
HFD-623/U. Atwal, Ph.D./ 8/1/97
HFD-623/V. Sayeed, Ph.D./ 8/5/97
X:\NEW\FIRMSNZ\TRIGEN\LTRS&REV\40189.RV3
F/T by:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040189

BIOEQUIVALENCE REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

ANDA 40-189

Trigen Laboratories, Inc.
Attention: Rajan Embran
207 Kiley Drive
Salisbury MD 21801

FEB 25 1997

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Methylprednisolone Tablets USP, 4 mg and 8 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-189

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Attention: Rajan Embran
207 Kiley Drive
Salisbury MD 21801

FEB - 4 1997

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Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JAN 27 1997

Methylprednisolone Tablets	Trigen
4 mg and 8 mg Tablets	Salisbury, MD
ANDA #40189	Submission Date:
Reviewer: Moo Park	May 24, 1996
Filename: 40189sdw.596	

Review of an In Vivo Bioequivalence Study, Dissolution Data and a Waiver Request

I. Objectives

Review of:

- Two-way crossover *in vivo* bioequivalence study comparing Trigen's Methylprednisolone Tablets, 8 mg strength, to Upjohn's Medrol^{R} (methylprednisolone) Tablets, 8 mg strength, following administration of a 32 mg dose under fasting conditions.

- Dissolution data for 4 mg and 8 mg tablets.

- A waiver request for 4 mg tablets.

II. Background

Methylprednisolone is a synthetic glucocorticoid indicated for a variety of conditions including endocrine disorders, rheumatic disorders, collagen diseases, dermatologic diseases and allergic states. It is more potent as an anti-inflammatory steroid and induces less sodium and water retention than the parent prednisolone. The initial recommended dose of methylprednisolone ranges from 4-48 mg depending on the condition requiring treatment.

In general, corticosteroids are readily absorbed following oral administration. The bioavailability of methylprednisolone is approximately 82% due to a first pass effect. Approximately 77%

is bound to plasma proteins. Peak plasma levels occur at 1-2 hours. The plasma half-life is 3 to 4 hours.

Medrol Tablets are available as scored tablets in the following strengths: 2 mg, 4 mg, 8 mg, 16 mg, 24 mg and 32 mg.

III. Study Details

1. Protocol #941620
2. Applicant: Trigen, Salisbury, MD
3. Study sites:
   Clinical study:

   Analytical:

4. Investigators:
   Medical director:

5. Clinical study dates: 1/27/96-2/3/96

   Assay dates: 2/13/96-3/26/96

6. Study design: Open-label, randomized, two-way crossover design.

7. Subjects: This study enrolled 26 healthy male volunteers, 18-45 years of age, weighing at least 60 kg, who are within 15% of their ideal weights (Table of 'Desirable Weights of Adults', Metropolitan Life Insurance Company, 1983).

   Medical histories and demographic data, including name, sex, age, race, body weight (kg), height (cm), body build and smoking habits were recorded. Each subject received a complete physical examination and the laboratory tests of hematologic, hepatic and renal functions. Only medically healthy subjects with clinically normal laboratory profiles were enrolled in the study.

   Of the 26 healthy adult male volunteers enrolled in the study, one did not complete the crossover. Subject **No.** 23 was withdrawn from the study 6.4 days after Period 1 dosing

due to medical events (see medical Events section for details). Thus, a total of 25 subjects completed the crossover.

8. Product information:

(a) Test product #1: Trigen's Methylprednisolone Tablets, 8 mg strength.

Lot #TB-001
Batch size: tablets

(b) Reference product: Upjohn's Medrol[R] Tablets, 8 mg strength.

Lot #474XK
Expiration date: Feb, 2000

9. Dosing: Subjects received a single, oral 32 mg dose (4 tablets) with 240 mL of water after an overnight fast.

10. Food and fluid intake: Subjects were required to fast overnight before dosing and for 4 hours thereafter. Water was not permitted for 1 hour before and 1 hour after the dose, but was allowed at all other times. Standard meals were provided at 4 and approximately 9 hours after drug administration. During housing, meal plans were identical for both periods.

11. Housing: From the evening before dosing until after the 16-hour blood draw.

12. Washout period: Seven days.

13. Blood samples: Blood samples were collected as specified in the protocol at the following times: before dosing and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12 and 16 hours post-dose. All blood samples were processed as specified in the protocol. All plasma samples were shipped to the

ɔn dry ice.

14. IRB and informed consent: IRB approved the protocol and informed consent form.

15. Pharmacokinetic and statistical analysis: SAS-GLM procedures were used on AUCT, AUCI, CMAX, TMAX, KE, THALF and blood levels at each sampling points. The 90% confidence intervals (CI) were calculated for log-transformed AUCT, AUCI, and CMAX.

IV. Validation of Assay Method for Plasma Samples

V. In Vivo Results with Statistical Analysis

Of the 26 healthy adult male volunteers enrolled in the study, one did not complete the crossover. Subject #23 was withdrawn from the study 6.4 days after Period 1 dosing due to medical events (viral syndrome). Thus, a total of 25 subjects completed the crossover. Statistical analysis was performed on data from 24 subjects (subjects #1-22, 24 and 25) as specified in the protocol.

Protocol Deviations: There were 6 late blood samplings, which were insignificant. The Medical Director recommended that Subject #9 not have his 16-hour blood drawn in Period 1 due to medical events (vomiting at 11 and 15 hours postdose). The deviations were judged unlikely to affect the bioequivalence study.

Medical events: There were a total of 25 medical events reported (Test drug product: 9 events for 8 subjects; Reference drug product: 16 events for 7 subjects). Subject #23 was withdrawn from the study due to viral syndrome. Subject #9 registered 8 events on reference product.

1. Mean plasma levels

The plasma methylprednisolone level-time profiles for the test and reference products are comparable as shown in Table 1 and Fig. P-1. Mean peak concentrations are 189 ng/mL and 196 ng/mL at 2 hours postdose for the test and reference products, respectively.

Table 5. MEAN PLASMA METHYLPREDNISOLONE LEVELS FOR TEST AND REFERENCE PRODUCTS
UNIT: PLASMA LEVEL=NG/ML TIME=HRS
MEAN1=TEST; MEAN2=REFERENCE; RMEAN12=MEAN1/MEAN2 RATIO
TEST LOT #(TRIGEN); REF LOT#(UPJOHN)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.25	11.94	23.03	9.35	21.85	1.28
0.5	61.93	65.37	67.80	54.74	0.91
0.75	115.95	87.50	118.67	62.96	0.98
1	146.45	87.66	155.97	63.05	0.94
1.5	179.86	62.19	180.76	52.21	1.00
2	189.23	43.05	194.69	47.35	0.97
2.5	183.81	35.08	189.44	39.12	0.97
3	176.11	37.54	180.80	38.12	0.97
4	148.26	35.59	151.41	48.34	0.98
5	121.02	41.03	114.73	39.81	1.05
6	87.44	33.68	83.74	33.75	1.04
8	47.74	23.70	44.35	22.62	1.08
10	24.62	16.23	22.28	15.73	1.10
12	12.10	12.19	11.09	10.72	1.09
16	2.26	4.66	0.97	3.31	2.34

2. Pharmacokinetic parameters

Arithmetic means and least squares means for the pharmacokinetic parameters are shown in Tables 6 and 7, respectively. The test/reference ratios for all the parameters are within 0.8-1.2.

Table 8 shows the 90% confidence intervals for LAUCT, LAUCI and LCMAX, which are all within 80-125%.

Table 6. ARITHMETIC MEANS AND RATIOS
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	1122.67	314.04	1110.71	300.31	1.01
AUCT	1079.58	309.63	1062.42	284.38	1.02
CMAX	210.82	53.53	216.14	39.26	0.98
KE	0.33	0.06	0.33	0.06	0.98
LAUCI	1081.25	0.28	1071.10	0.28	1.01
LAUCT	1037.27	0.29	1024.97	0.28	1.01
LCMAX	205.22	0.23	212.75	0.18	0.96
THALF	2.18	0.40	2.15	0.43	1.01
TMAX	2.31	1.13	2.06	0.80	1.12

Table 7. LSMEANS AND RATIOS
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

	LSM1	LSM2	RLSM12
PARAMETER			
AUCI	1122.67	1110.71	1.01
AUCT	1079.58	1062.42	1.02
CMAX	210.82	216.14	0.98
LAUCI	1081.25	1071.10	1.01
LAUCT	1037.27	1024.97	1.01
LCMAX	205.22	212.75	0.96

Table 8. LSMEANS AND 90% CONFIDENCE INTERVALS
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

	LSM1	LSM2	LOWCI12	UPPCI12
PARAMETER				
AUCI	1122.67	1110.71	96.94	105.21
AUCT	1079.58	1062.42	97.37	105.87
CMAX	210.82	216.14	91.44	103.64
LAUCI	1081.25	1071.10	97.44	104.58
LAUCT	1037.27	1024.97	97.64	104.89
LCMAX	205.22	212.75	91.37	101.83

3. Test/Reference ratios for individual subjects

The test/reference ratios for AUCT, AUCI, CMAX, TMAX, KE and THALF are listed in Table 9. Mean ratios are shown in Table 10.

Table 9. TEST PRODUCT/REFERENCE PRODUCT RATIOS FOR INDIVIDUAL SUBJECTS

OBS	SUB	SEQ	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
1	1	2						
2	2	2						
3	3	2						
4	4	1						
5	5	1						
6	6	1						
7	7	2						
8	8	2						
9	9	2						
10	10	1						
11	11	1						
12	12	2						
13	13	2						
14	14	1						
15	15	1						
16	16	2						
17	17	1						
18	18	2						
19	19	1						
20	20	1						
21	21	1						
22	22	2						
23	24	2						
24	25	1						

Table 10. STATISTICS ON THE TEST/REFERENCE RATIOS

Variable	N	Mean	Std Dev	Minimum	Maximum
RAUCT12	24	1.02	0.14	0.80	1.49
RAUCI12	24	1.02	0.13	0.81	1.44
RCMAX12	24	0.98	0.18	0.70	1.49
RTMAX12	24	1.36	1.02	0.25	5.00
RKE12	24	0.99	0.09	0.83	1.18
RTHALF12	24	1.02	0.09	0.85	1.20

4. AUCT/AUCI ratio for individual subjects

AUCT/AUCI ratios are listed in Table 11 for each subject and treatment combinations.

Table 11. AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS

OBS	SUB	TRT	AUCRATIO
1	1	1	
2	2	1	
3	3	1	
4	4	1	
5	5	1	
6	6	1	
7	7	1	
8	8	1	
9	9	1	
10	10	1	
11	11	1	
12	12	1	
13	13	1	
14	14	1	
15	15	1	
16	16	1	
17	17	1	
18	18	1	
19	19	1	
20	20	1	
21	21	1	
22	22	1	
23	24	1	
24	25	1	
25	1	2	
26	2	2	
27	3	2	
28	4	2	
29	5	2	
30	6	2	
31	7	2	
32	8	2	
33	9	2	
34	10	2	
35	11	2	
36	12	2	
37	13	2	
38	14	2	
39	15	2	
40	16	2	
41	17	2	
42	18	2	
43	19	2	
44	20	2	
45	21	2	
46	22	2	
47	24	2	
48	25	2	

VI. Product Information

1. Formulation

Test formulations for the 4 mg and 8 mg tablets are shown in Table 12. Two test formulations are proportional in active and inactive ingredients. Inactive ingredients of the reference product consist of calcium stearate, corn starch, lactose, mineral oil, sorbic acid, sucrose, and other inactive ingredients.

Table 12. Test Formulations

Ingredient	4 mg Strength mg/tablet	8 mg Strength mg/tablet
Methylprednisolone USP	4	8
Pregelatinized Starch		
Lactose Anhydrous NF		
Sodium Starch Glycolate NF		
Microcrystalline Cellulose		
Sodium Lauryl Sulfate		
Colloidal Silicon Dioxide		
Magnesium Stearate		
Total	100	200

2. Assay and content uniformity

Table 13 summarizes assay and content uniformity data for the test and reference products.

Table 13. Assay and Content Uniformity

Product	Assay, %	Content Uniformity (%CV)
Test (Trigen), 4 mg, #TB-003	97.3	98.1 (1.0)
Reference (Upjohn), 4 mg, #383JX Exp. Date:Jan, 2000	98.3	103.9 (1.8)
Test (Trigen), 8 mg, #TB-001	99.2	100.8 (1.0)
Reference (Upjohn), 8 mg, #474XK Exp. Date:Feb, 2000	95.1	98.5 (1.7)

VII. Dissolution

Test and reference products met USP dissolution specifications as shown in Table 14. USP dissolution specifications are shown below:

Medium and Volume	water; 900 mL
Apparatus and rpm	2 (paddle); 50 rpm
Time	30 min
Tolerances	NLT (Q)

VIII. Waiver Request

The applicant requested a waiver for the 4 mg tablets. Based on the acceptable *in vivo* and *in vitro* data and proportionality of formulations, the waiver for the 4 mg tablets is granted.

IX. Comments

1. Of the 26 healthy adult male volunteers enrolled, 25 subjects completed the crossover. Statistical analysis was performed on data from 24 subjects as specified in the protocol.

2. The plasma methylprednisolone level-time profiles for the

test and reference products are comparable. Mean peak concentrations are 189 ng/mL and 196 ng/mL at 2 hours postdose for the test and reference products, respectively.

The 90% confidence intervals for LAUCT, LAUCI and LCMAX are all within 80-125%.

3. Assay method validation: Pre-study and within-study validations are acceptable.

4. Test products (4 mg and 8 mg strengths) met USP dissolution specifications.

5. Formulations: Two test formulations, 4 mg and 8 mg tablets, are proportional in active and inactive ingredients.

6. There was no severe medical event which required a clinical action except subject #23 who was discontinued from the study due to viral syndrome.

7. The batch size of the bio-batch was tablets.

8. Waiver is granted for the 4 mg tablets.

X. Deficiency

None.

XI. Recommendations

1. The *in vivo* bioequivalence study conducted under fasting conditions by Trigen on its Methylprednisolone Tablets, 8 mg strength, lot #TB-001, comparing it to Upjohn's Medrol^{R} Tablets, 8 mg strength, lot #474XK, has been found acceptable. The study demonstrates that Trigen's Methylprednisolone Tablets, 8 mg strength, is bioequivalent to the reference product, Medrol^{R} Tablets, 8 mg strength.

2. The USP dissolution testing conducted by Trigen on its Methylprednisolone Tablets, 8 mg strength, lot #TB-001, and 4 mg strength, lot #TB-003, is acceptable. The formulation for the 4 mg strength tablets is proportionally similar to the 8 mg strength tablets of the test product which

underwent an acceptable bioequivalence study (submission date: 5/24/96). The waiver of *in vivo* bioequivalence study requirements for the 4 mg strength tablets of the test product is granted. The 4 mg strength tablets of the test product are therefore deemed bioequivalent to Upjohn's Medrol®, 4 mg strength tablets.

3. The USP dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 Apparatus 2 (Paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

4. From the bioequivalence point of view, the firm met the *in vivo* bioequivalence study and *in vitro* dissolution testing requirements and the study is approvable.

The firm should be informed of the recommendations.

Moo Park, Ph.D.
Chemist, Review Branch III
Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE
Ramakant M. Mhatre, Ph.D. 12/31/96
Team Leader, Review Branch III
Division of Bioequivalence

Concur: _____ Date: 1/27/97
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

cc: ANDA #40-189 (original, duplicate), Park, Drug File, Division File

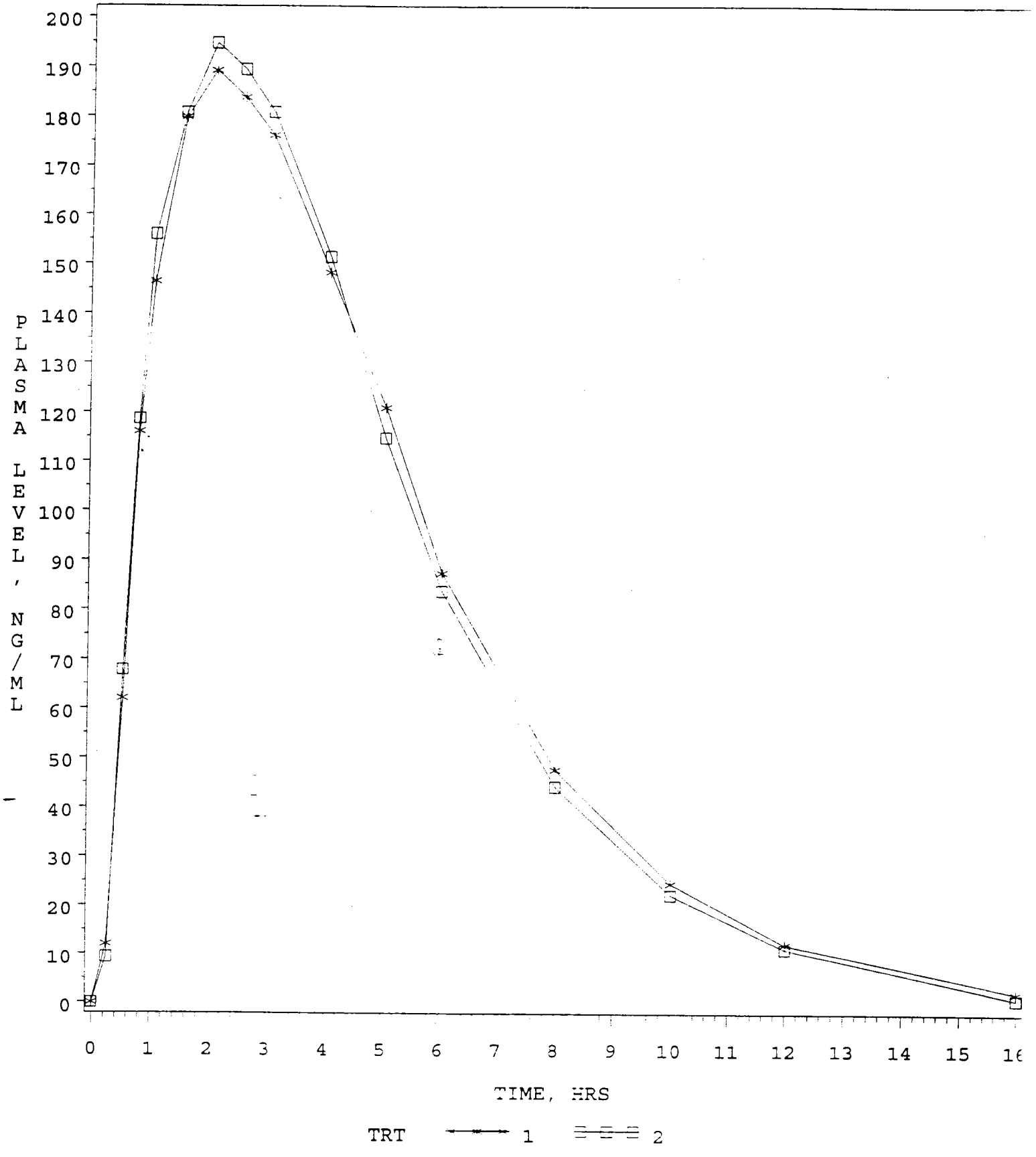
File history: Draft (11/20/96); Final (12/24/96)

Table 14. *In Vitro* Dissolution Testing Data						
I. General Information						
Drug Product (Generic Name)	Methylprednisolone Tablets					
Strength	4 mg and 8 mg Tablets					
ANDA Number	40-189					
Applicant	Trigen					
Reference Drug Product	Upjohn's Medrol®, 4 mg and 8 mg Tablets					
II. USP Method for Dissolution Testing						
Medium and Volume	water; 900 mL					
Apparatus and rpm	2 (paddle); 50 rpm					
Time	30 min					
Tolerances	NLT (Q)					
Assay Method						
III. Dissolution Data (%)						
Time	Test Product Lot No:TB-003 Strength:4 mg No of Units:12			Reference Product Lot No:383JX Strength:4 mg No of Units:12		
Min	Mean	Range	%CV	Mean	Range	%CV
15	90		2.9	88.8		2.8
30	91		2.1	88.3		1.6
Time	Test Product Lot No:TB-001 Strength:8 mg No of Units:12			Reference Product Lot No:474XK Strength:8 mg No of Units:12		
Min	Mean	Range	%CV	Mean	Range	%CV

15	93		1.9	102		2
30	95		0.6	101		1

FIG P-1. PLASMA METHYLPREDNISOLONE LEVELS

METHYLPREDNISOLONE TABLETS, 8 MG, ANDA #40-189
UNDER FASTING CONDITIONS
DOSE=4 X 8 MG



1=TEST PRODUCT(TRIGEN) 2=REFERENCE PRODUCT(UPJOHN)